Decision Summary

CMS is seeking public comment on our proposed determination that there is insufficient evidence to conclude that the use of nesiritide for the treatment of chronic heart failure is reasonable and necessary for Medicare beneficiaries.

Accordingly, we propose to issue a national coverage determination (NCD) denying coverage of nesiritide for the treatment of chronic heart failure in Medicare beneficiaries. We do not propose to change existing coverage of nesiritide for acute(ly) decompensated heart failure.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File: CAG #00289N
Nesiritide for Heart Failure Patients

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SUBJECT: Proposed Coverage Decision Memorandum for Nesiritide for Heart Failure Patients
DATE: December 2, 2005

I. Proposed Decision

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II. Background

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Cardiac decompensation, which is a manifestation of heart failure, is characterized by signs and symptoms of interstitial volume overload and/or inadequate tissue perfusion. The cardinal manifestations of heart failure are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time. Some patients have exercise intolerance but little evidence of fluid retention, whereas others primarily complain of edema and report few symptoms of dyspnea or fatigue. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term "heart failure" is preferred over the older term "congestive heart failure." (Harrison's Principles of Internal Medicine, 16th Edition, 2005).

Epidemiology and Disease Burden

Heart failure is growing in incidence and prevalence within the Medicare population and is associated with rising mortality rates. Though trends primarily reflect the strong association between heart failure and advancing age, they also are influenced by the rising prevalence of precursors such as diabetes, hypertension, and dyslipidemia within industrialized societies and the improved long-term survival of patients with ischemic and other forms of heart disease.

Heart failure affects nearly 5 million Americans, and over 550,000 new cases are diagnosed each year (American Heart Association, 2005). Heart failure is primarily a disease of the elderly. Approximately 78% of men and 85% of women with heart failure are 65 years of age or older; the median age of persons hospitalized with heart failure is 76 years. It accounts for nearly 1 million hospitalizations, causes nearly 50,000 deaths per year (Harrison's Principles of Internal Medicine 16th Edition, 2005), and is a contributory cause to over 260,000 deaths annually. As the US population ages over the next several decades, it is anticipated that the societal burden of heart failure will continue to rise at a rapid rate (Rich, 2001).

The annual incidence of new cases of heart failure rises from less than 1 per 1000 patient-years younger than age 45, to 10 per 1000 patient-years older than age 65, to 30 per 1000 patient-years older than age 85 (Goldman, 2004). Although the relative incidence and prevalence of heart failure are lower in women than in men, women constitute at least half of the cases because of their longer life expectancy.

Heart failure is the underlying reason for 12 to 15 million office visits and 6.5 million hospital days each year (O'Connell, 2000). During the past 10 years, the annual number of hospitalizations has increased from approximately 550,000 to nearly 900,000 for heart failure as a primary diagnosis, and from 1.7 to 2.6 million for heart failure as a primary or secondary diagnosis (Haldeman, Croft, Giles, Rashidee; 1999). The number of deaths has increased steadily despite advances in treatment.

Despite advances in therapy, the prognosis of patients with heart failure is poor. For those patients that survive the acute onset of heart failure, approximately only 35% of men and 50% of women survive after 5 years. Although it is difficult to predict prognosis, patients with symptoms at rest (class IV) have a 30 to 70% annual mortality rate, patients symptomatic with mild activity (class III) have mortality rates of 10 to 20% annually, and those patients symptomatic only with moderate activity (class II) have a 5 to 10% annual mortality rate. Mortality rates are higher in older patients, men, and patients with reduced ejection fractions and underlying coronary heart disease.

Disease Process
Heart failure may occur as a result of impaired myocardial contractility, increased ventricular stiffness, or impaired myocardial relaxation, a variety of other cardiac abnormalities, or states in which the heart is unable to compensate for increased peripheral blood flow or metabolic requirements. For adults, left ventricular involvement is almost always present even if the manifestations are primarily those of right ventricular dysfunction (fluid retention without dyspnea or rales). Heart failure may result from an acute insult to cardiac function, such as a large myocardial infarction (MI), or, more commonly, from a chronic process. In the United States, ischemic heart disease accounts for three-quarters of all cases. Cardiomyopathies are the second most frequent cause, followed by congenital, valvular, and hypertensive diseases.

Depending on the patient's course and clinical setting, heart failure can be classified into different groups. These groups are categorized as: systolic or diastolic dysfunction; high output or low output; acute or chronic; right-sided or left-sided; and forward or backward. The main distinction between systolic and diastolic heart failure is the inability of the ventricle to contract normally and expel sufficient blood (systolic dysfunction) or to relax and fill normally (diastolic dysfunction). Systolic dysfunction results in inadequate cardiac output and manifests itself as symptoms related to hypoperfusion. Diastolic dysfunction, which accounts for 20 to 40% of cases of heart failure, is primarily related to resistance to ventricular filling and is generally associated with prolonged ventricular relaxation time. Diastolic heart failure occurs more frequently in women than in men, especially in elderly women. In most patients with heart failure, abnormalities exist in both contraction as well as relaxation of the ventricles. Combined systolic and diastolic abnormalities are common.

Interaction of the Intervention with the Disease Process

Treatment Options
Due to the multiple etiologies and the hemodynamic features of heart failure, there is no simple rule for treatment. The five major components of treatment are: (1) general measures; (2) correction of the underlying cause(s); (3) removal of the precipitating cause(s); (4) prevention of deterioration of cardiac function and; (5) control of the heart failure state. General measures include a moderate dietary sodium restriction, daily weighing (to monitor fluid retention), education about diet and medication compliance, and environmental precautions. Control of the other four components usually involves the use of medication.

To control excess fluid, diuretics are commonly used along with diet modification. Medications such as angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), aldosterone antagonists, and beta blockers are used to prevent the deterioration of myocardial function. Medications used to enhance myocardial contractility include digitalis, sympathomimetic amines, and phosphodiesterase inhibitors. Other groups of medications commonly used in the treatment of heart failure include vasodilators, anticoagulants, and medications used to manage arrhythmias.

For patients suffering with refractory heart failure (i.e., when the response to ordinary treatment is inadequate), more aggressive management may be required. Before these measures are taken, underlying or precipitating causes that may be amenable to specific surgical or medical treatment should be ruled out. Also, complications from overly vigorous therapy should be addressed. Once these have been excluded, urgent treatment necessitating hospitalization and the use of intravenously-administered vasodilators such as nitroglycerin or phosphodiesterase inhibitors may be required. Patients suffering from refractory heart failure can have an acute exacerbation of the condition. This is known as acute(ly) decompensated heart failure (ADHF).

ADHF is a life-threatening condition for which there are limited treatment options. Patients suffering from advanced ADHF have a 30% risk of mortality within one year (Lee, Rouleau, 2003). On August 10, 2001, the FDA approved nesiritide (Natrecor®) for the intravenous treatment of ADHF patients who have dyspnea at rest or with minimal activities. In this population, the use of nesiritide reduces pulmonary wedge capillary pressure and improves dyspnea. Nesiritide is a human B-type natriuretic peptide derived from E. coli bacteria using recombinant DNA. It has the same 32-amino-acid-sequence as the endogenous peptide, which is produced by the ventricular myocardium. Nesiritide's mechanism of action was demonstrated *in vitro* by relaxing human arterial and venous tissue preparations that were precontracted with either endothelin-1 or the alpha-adrenergic agonist, phenylephrine. Nesiritide is administered as an intravenous bolus, followed by continuous infusion. Because of the potential for hypotension, blood pressure should be monitored closely during nesiritide administration. One of the routes of excretion of nesiritide is through the kidneys.

Recently published medical literature expresses concerns about the safety of nesiritide. Specifically, renal dysfunction (Sackner-Bernstein, Skopicki, Aaronson, 2005) and a trend toward increased mortality (Sackner-Bernstein, Kowalski, Fox, Aaronson, 2005) have been reported. Also of concern is the possible misuse of nesiritide. Though the FDA indication is for the treatment of patients with ADHF, some providers are also using nesiritide intermittently to treat chronic heart failure. The authors express concerns that this off-label use of nesiritide for chronic heart failure poses significant risk to patients.

Because of concerns on nesiritide's safety profile as well as its appropriate use, Scios/Johnson & Johnson (J&J) established an expert panel of cardiologists and heart failure clinicians to review usage and safety data. This expert group, referred to as the "Nesiritide Advisory Panel," first met on June 8, 2005, and considered renal insufficiency, mortality, and the effectiveness of nesiritide. The panel issued a consensus statement, provided advice on the ongoing and planned clinical development program, made recommendations about the appropriate use of the drug, and recommended that Scios immediately conduct an educational campaign. This campaign should inform physicians about the conditions and circumstances in which nesiritide should and should not be used and should ensure that current and future marketing and sales activities are consistent with the educational program. The Panel's conclusions were sent out as a "Dear Healthcare Provider Letter" on July 13, 2005.

The reports of increased risk of renal disease, increased mortality, and the Nesiritide Advisory Panel recommendations raised concerns at CMS and led to our accepting the external request to review the evidence on the off-label use of nesiritide. An off-label use of a drug is a use that is not included as an indication on the drug's label as approved by the FDA. FDA-approved drugs may be covered under Medicare for off-label use if the contractor determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice. We do not review the labeled indications for nesiritide in this NCD.

III. History of Medicare Coverage

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services). Nesiritide is an FDA-approved drug for intravenous use, and is not self-administered. Nesiritide is considered to be within the following two benefit categories: inpatient hospital services (§1861 (b)(2)); and drugs and biologicals which are not usually self-administered by the patient may be considered to be within the benefit category of "incident to" a physician's service rendered to hospital outpatients (§1861(s)(2)(B)).

Medicare does not currently have a National Coverage Determination for nesiritide.

IV. Timeline of Recent Activities

June 29, 2005	CMS opened an NCD to evaluate the use of nesiritide in the Medicare population in response to an external request to determine if nesiritide is reasonable and necessary for the treatment of chronic heart failure in beneficiaries. The initial 30-day public comment period began.
July 29, 2005	End of public comment period for tracking sheet. 136 comments received.

V. FDA Status

On August 10, 2001, the FDA approved Natrecor® (nesiritide) with the following labeled indication:

"Natrecor (nesiritide) is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of Natrecor reduced pulmonary capillary wedge pressure and improved dyspnea."

In addition to effects on symptoms, the FDA reviewed hemodynamic variables including pulmonary capillary wedge pressure, right atrial pressure, systolic blood pressure, pulmonary vascular resistance, systemic vascular resistance, and cardiac output. The FDA also studied other variables including renal and cardiovascular status. In assessing renal status, the Vasodilation in the Management of Acute Congestive Heart Failure trial (VMAC) revealed that nesiritide affected the renal status in susceptible individuals, and sometimes resulted in azotemia. When nesiritide was initiated at dosages higher than 0.01 µg/kg/min, there was an increased rate of elevated serum creatinine over baseline compared to standard therapy. In the 30-day follow up period in the VMAC trial, five patients in the nitroglycerin group and nine patients in the nesiritide group required first-time dialysis.

Subsequent label revisions on July 2, 2004, April 20, 2005, and April 29, 2005, reflected changes in dosing instructions and mortality data. On July 13, 2005, Scios and the FDA notified healthcare professionals about the recommendations of the Nesiritide Advisory Panel regarding nesiritide. These recommendations can be found in the section VII.B.7 of this document.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. An improved net health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

VII. Evidence

A. Introduction

We are providing a summary of the evidence we considered during our review. We will, of course, consider additional evidence submitted through the public comment period. The evidence reviewed to date in this proposed decision memorandum includes the published medical literature on pertinent clinical trials of nesiritide.

A variety of outcome measures may be appropriate, depending on the setting (acute or chronic). Relief of dyspnea, a subjective judgment, is a short -term outcome measure. Reduction of mortality, hospitalization, development of complications, or the need for other therapies are longer term outcome measures that are more objectively measured.

B. Discussion of Evidence Reviewed

1. Question

Is the quality of evidence adequate to conclude that the use of nesiritide to treat chronic heart failure improves net health outcomes for Medicare beneficiaries?

2. External technology assessments

We did not request an external technology assessment on this issue and are unaware of any assessments that were conducted independently.

3. Internal technology assessments

Literature search methods

Medical literature was identified using MEDLINE, Cochrane Collaborative, and a number of cardiology textbooks. Peer-reviewed articles written in English were reviewed. Search terms included: nesiritide, Natrecor®, heart failure, congestive heart failure, intermittent heart failure, intermittent chronic heart failure, and intermittent congestive heart failure. We identified 12 references pertaining to the intermittent use of nesiritide for chronic heart failure. Three publications were peer-reviewed articles. One article was a case study (Josephson, Barnett 2004), another article was of a non-randomized prospective study (Sheik-Taha 2005), and the final peer-reviewed article was a prospective randomized study (FUSION I) that is often quoted by proponents of the use of intermittent nesiritide (Yancy 2004). There were also numerous abstracts advocating intermittent nesiritide usage (Chung, Menon, Daly et al. 2004; Altschul, Masciello et al. 2003, Altschul, Masciello, et al. 2002; Mulki, Pisano et al. 2003; Squiers, Vora 2003; Bhaskaran, Siegel et al. 2003). There was one literature review article (Silver 2004), and two commentaries (Sackner-Bernstein, Skopicki 2005; Sackner-Bernstein, Kowalski 2005).

Josephson and Barnett followed 35 patients receiving nesiritide infusions in an outpatient heart failure program involving approximately 475 infusions (Josephson, Barnett, 2004). All patients exhibited decompensated heart failure refractory to standard treatment. Baseline characteristics, comorbidities, and risk assessment scores utilizing the prognostic factors in the FUSION I trial were incorporated. Based on risk assessment scores, patients were divided into two groups: a high-risk group (51%) and a low-risk group (49%). Using a follow-up questionnaire, 28 patients (80%) reported improved quality of life and improved symptomatic relief following nesiritide infusion. At twelve weeks post-infusion, 71% of patients in the study were alive and had no hospitalizations (compared to 52% in the FUSION I study). A 29% reduction in hospital stay compared to the year prior with no infusional use of nesiritide (six-and-one-half days compared to nine days) was reported as well. The FUSION I study noted 4.6% mortality in the high-risk group at 12 weeks versus 17.4% mortality in the high-risk standard care patients. A similar mortality rate was noted in the Josephson Barnett study for patients receiving nesiritide at 12 weeks.

The FUSION I study was one of the first large-scale clinical trials to test the safety and feasibility of using serial infusions of nesiritide for heart failure in an outpatient setting (Yancy, Saltzberg, Berkowitz, Berolet, Vijayaraghavan, Burnahm et al. 2004). This study is often quoted by those who advocate the use of intermittent nesiritide for the treatment of chronic heart failure. In this open label study, 210 patients suffering from ADHF were assigned to one of three treatment groups: (1) usual care as determined by the investigating physician (n=69); (2) usual care plus 0.005 µg/kg/min of nesiritide given for four to six hours, preceded by a 1.0 µg/kg bolus (n=72); or (3) usual care plus 0.01 µg/kg/min of nesiritide given for four to six hours, preceded by a 2.0 µg/kg bolus (n=69). Primary endpoints included adverse events, serious adverse events (including all-cause death and hospitalization), vital signs, and laboratory assessment. The Minnesota Living with Heart Failure questionnaire was also used. The study treatment period was 12 weeks, with an additional four weeks of follow-up. No statistically significant differences could be found between treatment groups when evaluating deaths or hospitalizations, though patients receiving nesiritide showed trends for more days alive and out of the hospital compared with patients receiving usual care. A prospective analysis defining higher risk subgroups noted a significant decrease in cardiovascular events.

Sheikh-Taha evaluated the benefit of outpatient intermittent nesiritide therapy in chronic heart failure (Sheikh-Taha, 2005). This was a single-center, nonrandomized, open label, prospective study of 14 patients with chronic left ventricular systolic dysfunction undergoing long-term infusion with dobutamine or milrinone at an outpatient cardiac infusion unit. Inclusion criteria included patients who were 18 years of age or older, had refractory symptoms compatible with NYHA class III or IV heart failure, and were intolerant of or refractory to intermittent IV inotropic therapy with dobutamine or milrinone. The patients received "maximum oral therapy with diuretics; ACE inhibitors, angiotensin receptor blockers, or the combination of hydralazine and isosorbide dinitrate; beta blockers; nitrates; and spironolactone." Patients were excluded if their systolic blood pressure was consistently less than 90 mm Hg or they had biventricular pacemaker placement. At each visit to the cardiac infusion unit, patients received a bolus IV infusion of nesiritide 2µg/kg, followed by 0.01 µg/kg/min given over four to six hours. The patients also received a four-to-six-hour infusion of IV dobutamine 4-6 µg/kg/min or milrinone (loading dose of 50 µg/kg given over 10 min, followed by a maintenance infusion of 0.175 -0.375 µg/kg/min). Treatment was administered either once or twice a week, depending on symptoms. Patients were followed for three months after beginning nesiritide therapy. Primary endpoints included changes in NYHA class, hospitalization for worsening heart failure symptoms, frequency of visits to the heart failure center, and any adverse effects due to nesiritide. The results of the study revealed no statistically significant improvement in NYHA classification during the trial. Patients were found to have fewer hospitalizations due to exacerbation of heart failure after starting nesiritide therapy and the difference was statistically significant (p=0.0253). The number of visits to the heart failure clinic for all patients declined on nesiritide therapy; however the difference was not statistically significant (0.0749).

A number of study abstracts evaluating the intermittent use of nesiritide in chronic heart failure were located. Some have been presented at scientific meetings (Chung, Menon, Daly et al. 2004; Altschul, Masciello, Massaro 2003). One of these (Chung et al. 2004) was a prospective open-label study with 19 subjects, while another (Altschul et al. 2003) was a retrospective study with 65 subjects. Though both studies showed clinical improvement, both also had significant methodological flaws. Other abstracts are also available (Altschul, Masciello, Massaro 2002; Mulki, Pisano, Colleen, et al. 2003; Squiers Vora, 2003; Golden, Fallick, Barnett 2002; Bhaskaran, Siegel, Barker, et al. 2003). For these studies, subject size ranged between 14 and 30 patients. Case studies, open-label trials, or retrospective reviews were the research designs employed. These abstracts report clinical benefits to patients, but as noted above, they also are plagued with significant methodological shortcomings. When full articles based on these abstracts are published, they may be assessed further.

Sackner-Bernstein et al. also noted increased risk of worsening renal function in patients treated with nesiritide for ADHF (Sackner-Bernstein, Skopicki, Aaronson, 2005). Using electronic and manual searches, as well as clinical trial data obtained from the FDA, the authors located five randomized clinical trials and performed a meta-analysis that compared nesiritide with either placebo or active control for ADHF (n=1269). The study revealed that using the FDA-approved doses of nesiritide significantly increased the risk of worsening renal function compared to non-inotrope-based control (RR 1.52, p=0.003), or any control therapy, including non-inotrope and inotrope-based therapy (RR 1.54, p=0.001). Even low-dose nesiritide significantly increased risk compared to non-inotrope and inotrope-based controls (p=0.012 and p=0.006 respectively). This study did note that there was no difference in the need for dialysis between therapeutic groups.

Nesiritide was also noted to cause hypotension. In Sackner-Bernstein's review of the VMAC trial, patients given the recommended bolus dose (2 µg/kg), followed by a 0.01 µg/kg/min infusion, had an incidence of symptomatic hypotension in the first 24 hours that was similar to patients who received nitroglycerin. When hypotension occurred the duration of symptomatic hypotension was longer with nesiritide than with nitroglycerin. Also, in earlier trials when nesiritide was initiated at doses higher than 2 µg/kg, followed by a 0.01 µg/kg/min infusion, there were more hypotensive episodes. Furthermore, these episodes were of greater intensity, duration, more likely to be symptomatic, and also more likely to require medical interventions.

Sackner-Bernstein and colleagues, using primary reports of completed clinical trials obtained from the FDA and sources, obtained 12 randomized double-blind controlled trials and performed a pooled analysis evaluating the use of nesiritide in patients with ADHF (Sackner-Bernstein, Kowalski, Fox, Aaronson, 2005). Thirty-day survival was assessed by meta-analysis and Kaplan Meier analysis was used to determine risk of death. After excluding trials which did not meet criteria for the study, three trials remained (NSGET, VMAC, and PROACTION). In this analysis of these 3 trials, 485 patients were randomized to nesiritide and 377 were randomized to control therapy. The results of this study, which used a pooled analysis, revealed that deaths within 30 days tended to occur more often among the patient randomized to nesiritide therapy than to the randomized control group (RR 1.74, CI 0.97-3.12; p=0.059). No specific reason was given for this increased mortality in the nesiritide group.

4. MCAC

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

There are a number of guidelines available which encourage the use of nesiritide for ADHF (Task Force on Acute Heart Failure of the European Society of Cardiology; Institute for Clinical Systems Improvement 2004; ACC/AHA Guidelines 2005; University of Kentucky Nesiritide BNP Protocol). Most of these guidelines do not mention the intermittent use of nesiritide for chronic heart failure specifically, though they do note the role of nesiritide in patients with ADHF. ACC/AHA recently revealed its 2005 guidelines for heart failure. These guidelines note that nesiritide improves symptoms of acute heart failure, but the guidelines do not recommend the outpatient intermittent or continuous use of nesiritide for heart failure. Rather, the guidelines recommend more definitive studies in this setting as an adjunctive therapy.

CMS has contacted a number of national organizations that develop guidelines for nesiritide usage, and they replied that currently there is not sufficient evidence to support its intermittent use in chronic heart failure; however, there is adequate evidence demonstrating effectiveness in patients with ADHF.

6. Professional Society Position Statements

We have not found nor received professional society position statements on this topic.

7. Expert Opinion

Earlier this year (2005) Scios, the manufacturer of Natrecor® (nesiritide), convened the Nesiritide Advisory Panel to review and assess important data associated with acute heart failure and Natrecor®. In addition, the panel was tasked with providing guidance and counsel on the ongoing and planned clinical development program for the product as well as recommendations for use. The panel reviewed information submitted by Scios which included the original and current package inserts (dated August 2001 and April 2005, respectively), communications that Scios sent to physicians, recent papers by Sackner-Bernstein et al., and other nesiritide publications. After reviewing the data, the panel made recommendations to Scios. The panel's recommendations are the following:

1. The use of nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated congestive heart failure who have dyspnea at rest, as were the patients in the largest trial that led to approval of the drug (VMAC). Physicians considering the use of nesiritide should consider its efficacy in reducing dyspnea, the possible risk of the drug summarized above, and the availability of an alternative therapy to relieve the symptoms of congestive heart failure.
2. Nesiritide should not be used to replace diuretics. Furthermore, because sufficient evidence is not currently available to demonstrate benefit for the applications listed below, nesiritide should not be used:
    - For intermittent outpatient infusion
    - For scheduled repetitive use
    - To improve renal function
    - To enhance diuresis.
3. Scios should immediately undertake a pro-active educational program to inform physicians regarding the conditions and circumstances in which nesiritide should and should not be used, as described above. Sponsor-supported communications, including review articles of nesiritide, should reflect the above recommendations. Scios should ensure that current and future marketing and sales activities related to nesiritide are consistent with this educational program. (Scios, Inc. 2005)

8. Public Comments

Initial public comments

Initial Comment Period: June 29, 2005 - July 29, 2005

CMS received 136 comments during the public comment period. Fifty-two comments (38%) were from patients, family members or acquaintances of patients receiving outpatient nesiritide. Forty comments (29%) were from nurses, nurse practitioners, or clinical nurse specialists providing care at outpatient nesiritide clinics. Twenty-four comments (18%) were from physicians and 20 (15%) were from other health professionals. One comment included in this total was received representing two professional associations. The majority 133 (98%) of these comments supported coverage of nesiritide in the outpatient setting. Several commenters provided supplemental information and offered follow-up contact. No new published scientific evidence was submitted.

Public comments received as of July 29, 2005, are summarized below:

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- Patients, family members, or acquaintances of patients receiving nesiritide in the outpatient setting stated that nesiritide has reduced their hospital inpatient admissions and improved patients' quality of life dramatically. Many of the commenters requested that outpatient use of nesiritide continue to be covered and expressed fears about living without the drug.

- Physicians and nurses treating CHF patients with outpatient administration of nesiritide unanimously reported increased survival overall, improved quality of life, and reduced inpatient hospital admissions for these patients. Several health professionals commented that they had seen no renal complications in these patients as reported in the literature. One cardiologist further noted that the Nesiritide Advisory Panel did not recommend intermittent outpatient use because of lack of evidence, not because of safety concerns.

- One physician and one pharmacist opposed outpatient coverage of nesiritide. In particular, these commenters expressed concerns over the lack of safety and efficacy data supporting such use.

- Two professional associations jointly submitted one comment opposing outpatient coverage of nesiritide unless the infusions occur as part of randomized controlled trials (e.g.: FUSION II). These associations also stated their agreement with the Nesiritide Advisory Panel.

Twenty-seven commenters (20%) supported further research on the use of nesiritide in the outpatient setting.

Most of the public comments related personal experiences submitted by patients receiving nesiritide, and by their family members and medical personnel involved in the drug's administration. We recognize that they are reporting positive experiences associated with the use of nesiritide. However, individual anecdotal reports do not constitute sufficient evidence to disregard more methodologically rigorous data.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Nesiritide is an FDA-approved drug for intravenous use, and is not self-administered. Nesiritide is considered to be within the following two benefit categories: inpatient hospital services (§1861 (b)(2)); and drugs and biologicals which are not usually self-administered by the patient may be considered to be within the benefit category of "incident to" a physician's service rendered to hospital outpatients (§1861(s)(2)(B)). Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member," according to §1862(a)(1)(A) of the Social Security Act.

Question

Is the quality of evidence adequate to conclude that the use of nesiritide to treat chronic heart failure improves net health outcomes for Medicare beneficiaries?

Off-label Indications and Safety Concerns about Nesiritide

As summarized in the Evidence Table (Appendix A) and discussed above, the results of some of the articles we reviewed suggest that nesiritide therapy for chronic heart failure may reduce days of hospitalization and improve symptoms. However, this is not a consistent finding across all studies. For example, there was no reported change in NYHA class. Furthermore, nesiritide use was associated with worsened renal function and increased mortality.

Much of the reported research on the use of nesiritide for the intermittent treatment of chronic heart failure appears in abstracts and has not yet been published as full peer-reviewed journal articles. In general, abstracts do not provide sufficient information for us to evaluate the strength of the reported findings critically. As such, these abstracts do not constitute strong evidence and are given less weight than other evidence. The published articles supporting the off-label use of nesiritide for chronic heart failure are hampered by methodological shortcomings, including small sample size and the lack of long term outcome data.

Josephson, Barnett, 2004: This study has a number of limitations, including small sample size (n=35). Though patients were followed for two years, only 12-week mortality was reported, and only the one-year hospitalization rate was reported. Inclusion criteria were not provided, and no reporting of results based on high-risk versus low-risk status was included in the study.

Yancy, Saltzberg, Berkowitz, Berolet, Vijayaraghavan, Burnahm et al. 2004: This study has some methodological issues, including small sample size (n=210), short duration, open-label design, the use of "ill defined" usual care, and employment of a prospective analysis to define sub-groups (see Appendix A). Because of the limitations noted in this study, a second study (FUSION II) was initiated in 2004 (Yancy 2004). FUSION II, a double-blind, placebo-controlled trial, will use mortality/cardiorenal hospitalization as a composite end point. This study will randomly assign approximately 900 patients to either treatment with usual care plus nesiritide or usual care plus placebo. We will review those results when they become available.

Sheikh-Taha, 2005: No detailed information was provided about the tolerability of the drug, though course of treatment for two patients was altered due to hypotension secondary to nesiritide. This study is limited by its small sample size (n=14), open label design, lack of randomization, and lack of control group.

Sackner-Bernstein, Skopicki, Aaronson, 2005: A number of limitations were noted in this study, including the unavailability of primary data, the use of a single arbitrary definition of worsening renal function, the inability to identify and adjust for baseline differences in the treatment groups, and limited information on events or interventions that occurred after the treatment period.

These weaknesses, along with the incidence of renal dysfunction, the increased incidence of mortality, and the findings and recommendations of the Nesiritide Advisory Panel create substantial concerns about the net health outcomes associated with the use of this drug for chronic heart failure. Based on our analysis of the evidence to date, CMS proposes that Medicare coverage of nesiritide should be denied for the treatment of chronic heart failure.

IX. Proposed Conclusion

CMS is seeking public comment on our proposed determination that there is insufficient evidence to conclude that the use of nesiritide for the treatment of chronic heart failure is reasonable and necessary for Medicare beneficiaries.

Accordingly, we propose to issue a national coverage determination (NCD) denying coverage of nesiritide for the treatment of chronic heart failure in Medicare beneficiaries. We do not propose to change existing coverage of nesiritide for acute(ly) decompensated heart failure.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

APPENDIX A [PDF, 130KB]

APPENDIX B

General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.

Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).

Co-interventions or provision of care apart from the intervention under evaluation (performance bias).

Differential assessment of outcome (detection bias).

Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Net health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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